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UNIT 1: Human Health and Disease

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Level 3 Diploma in Medical Science

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Article adapted from: https://www.independent.co.uk/news/health/haemophilia-a-gene-therapy-cure-life-long-medication-drugs-blood-clot-condition-a8110921.html

Haemophilia gene therapy breakthrough sees patients taken off life-long medication

People with haemophilia have been effectively cured by a 'mind-blowing' gene therapy which means they can go without their tri-weekly treatment for the first time.

In haemophilia, any small cut can lead to excessive bleeding. It can also cause life-threatening internal bleeding, which can lead to joint damage and arthritis. There is no known cure for the condition.

Sufferers of the condition, which is inherited and mainly affects men, have very little of a blood clotting protein called Factor VIII.

Patients require injections of Factor VIII three times a week. Missing a treatment can have a serious impact on quality of life.

A medical paper shows that a small-scale clinical trial of a new type of gene therapy could replace this defective gene entirely.

The trial saw patients injected with a copy of the missing gene, which allowed cells to produce the missing Factor VIII.

All patients were able to stop regular treatment for the condition and most have nearly normal levels of the missing protein, Factor VIII, after having their progress followed for 19 months.

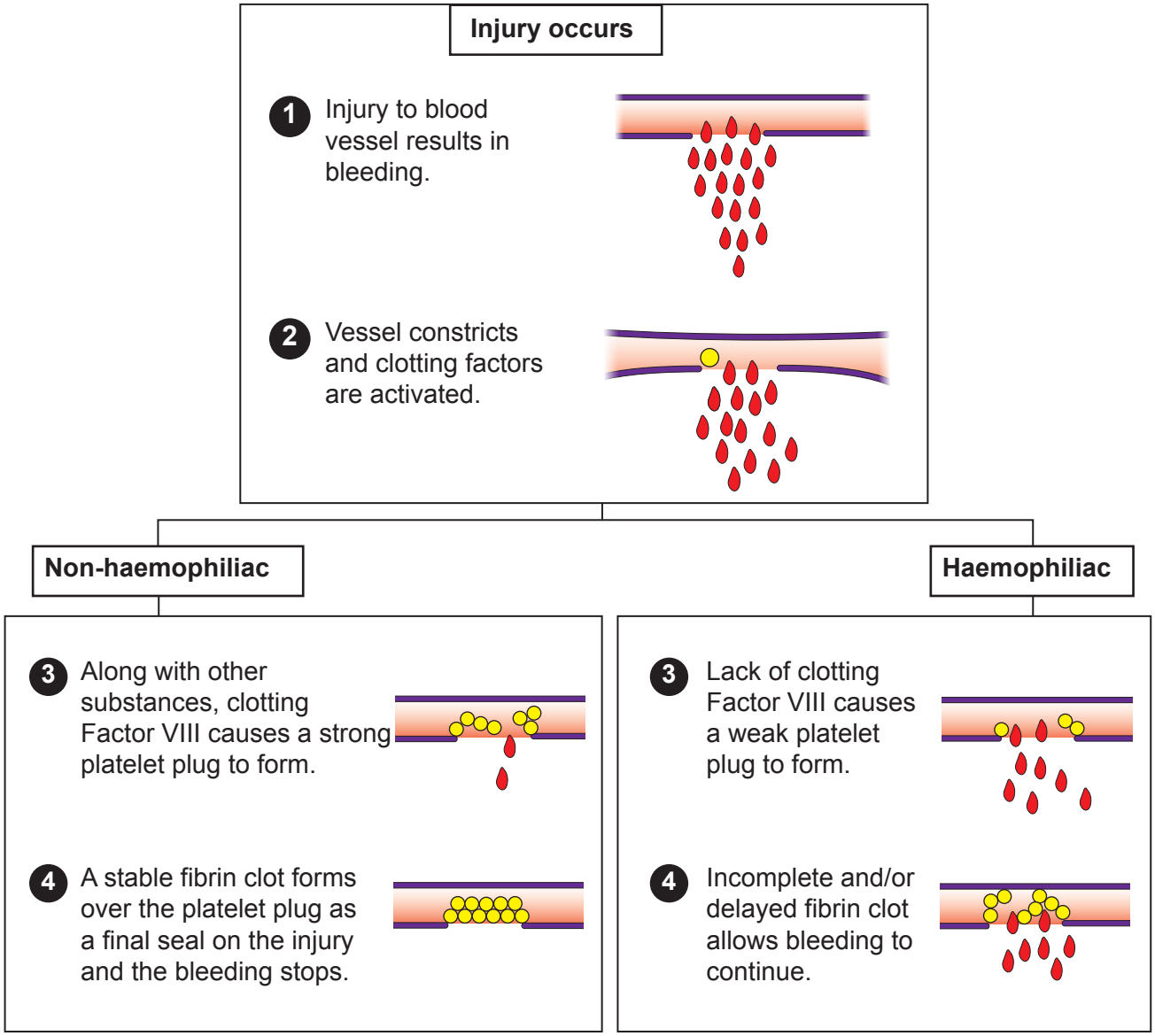
Further trials will now be carried out in the US, Europe, Africa and South America.

Haemophilia

Haemophilia is a rare condition that affects the blood's ability to clot.

Normally, when a person cuts themselves, clotting factors combine with thrombocytes to form a clot. However, people with haemophilia do not have as many clotting factors as normal. This means they bleed for longer than usual.

Figure 1: Response to blood vessel injury in a haemophiliac and non-haemophiliac.



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Turn over.

Causes

Haemophilia is caused by an inherited genetic mutation, which mainly affects males.

A genetic mutation is a permanent alteration in the DNA sequence that makes up a gene. This means that some of the body's processes will not work as they should. The type of mutation determines whether a person will experience mild, moderate or severe symptoms.

How the mutation is inherited

This mutation is found on the X chromosome, therefore there are five possible genotypes:

XX – Unaffected female
XX^h – Carrier female
X^hX^h – Haemophiliac female
XY – Unaffected male
X^hY – Haemophiliac male

If a carrier female and an unaffected male have a baby, there is a:

- one in four chance of having an unaffected baby boy
- one in four chance of having a baby boy with haemophilia
- one in four chance of having an unaffected baby girl
- one in four chance of having a baby girl with an affected X chromosome

Some female carriers sometimes have bleeding problems, such as heavy periods.

If a man with haemophilia has a child with an unaffected female:

- No sons will have haemophilia. This is because the son will always inherit an X chromosome from the mother, who in this case does not have the mutated gene.
- All daughters will be carriers of the mutated gene and may pass it on to their children.

If a female carrier and haemophiliac male have a baby, there is a:

- one in four chance of having an unaffected baby boy
- one in four chance of having a baby boy with haemophilia
- one in four chance of having a baby girl who is a carrier of haemophilia
- one in four chance of having a baby girl with haemophilia

This means it is possible for a female to have haemophilia, although it is very rare.

No family history

Studies have shown that in up to a third of new cases a boy is born with haemophilia even though there is no family history of the condition.

It is thought the mutation developed spontaneously in the boy's mother, grandmother or great-grandmother, but until then a male member of the family had never inherited the mutated gene.

How haemophilia affects the blood

Thrombocytes have a sticky surface that allows them to clump together to stop the flow of blood. They also need proteins called clotting factors that form a “web” around the thrombocytes, helping them to stay in place.

Several different clotting factors are present in the blood and mutation of their genes gives rise to several forms of haemophilia.

The mutated haemophilia gene causes a lack of clotting factors in blood. In haemophilia A there is not enough Factor VIII. In haemophilia B, there is not enough Factor IX.

Symptoms

The symptoms of haemophilia depend on the severity of the condition but usually involve prolonged bleeding which may occur spontaneously. For example, this could be:

- sudden nosebleeds
- bleeding gums
- joint bleeds
- muscle bleeds

The bleeding may also occur after a medical procedure, such as having a tooth removed.

Severity of haemophilia in children

Mild haemophilia

Children born with mild haemophilia may not have any symptoms for many years.

The condition usually only becomes apparent after a significant wound or surgery, which causes unusually prolonged bleeding.

Moderate haemophilia

Children with moderate haemophilia are affected in the same way as those with mild haemophilia, but also bruise easily. They may also have symptoms of internal bleeding around their joints, particularly if they have a knock or a fall. This is known as a joint bleed.

The symptoms usually begin with a tingling feeling and mild pain in the affected joint – most commonly the ankles, knees, and elbows. The shoulder, wrist, and hip joints can sometimes be affected.

If a joint bleed is not treated, it can lead to:

- severe joint pain
- stiffness
- the joint becoming hot, swollen, and tender

Severe haemophilia

The symptoms of severe haemophilia are like those of moderate haemophilia. However, joint bleeding is more frequent and severe.

Children with severe haemophilia have spontaneous bleeding where they start bleeding for no apparent reason.

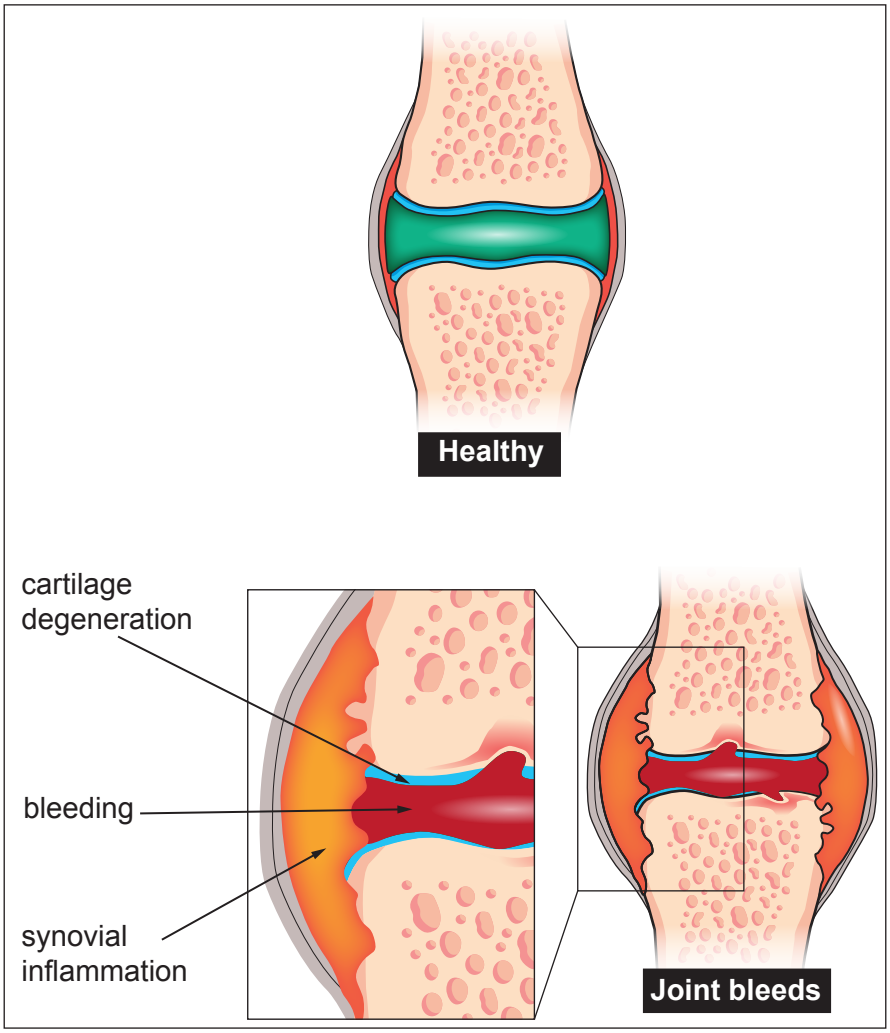
Without treatment, people with severe haemophilia can develop:

- joint deformity, which may require replacement surgery
- soft tissue bleeding
- serious internal bleeding

Joint bleeding and damage

Joint bleeds can damage the cartilage and the synovial membrane. The more damaged a joint is, the more vulnerable it is to bleed. Joint damage is more common in older adults with severe haemophilia. Surgery can be used to remove damaged synovial membrane so new tissue can grow. Serious damage to a joint may require a joint replacement.

Figure 2: Joint bleeding and damage caused by haemophilia.



Intracranial haemorrhage

There is a small risk of bleeding inside the skull, known as an intracranial haemorrhage, which is usually only caused by a head injury. It is estimated that 3% of people with moderate or severe haemophilia will have a spontaneous intracranial haemorrhage which should be treated as a medical emergency.

The symptoms of an intracranial haemorrhage include:

- severe headache
- stiff neck
- vomiting
- change in mental state
- speaking difficulties
- changes in vision
- loss of co-ordination and balance
- paralysis of some or all of the facial muscles

Treatment

The recommended treatment plan for haemophilia depends on the severity of the condition.

There are two main approaches to treatment:

- **Preventative treatment** – where medication is used to prevent episodes of bleeding and subsequent joint and muscle damage.

- **On-demand treatment** – where medication is used to treat an episode of prolonged bleeding.

Haemophilia is usually treated at a specialist haemophilia hospital department.

Preventative treatment

Most cases of haemophilia are severe and need preventative treatment. This involves regular injections of clotting factor.

If a child has haemophilia, parents will be trained to give the injections. The child will be taught how to inject themselves when they are older.

In some cases, medication may be administered through an implantable port, which can be surgically placed under the skin. This port is connected to a blood vessel near the heart, so sufferers do not need to try to find a vein for every injection.

Regular follow-up appointments with their care team are needed for monitoring.

Preventative treatment is continued for life. It may be possible for someone to change to on-demand treatment, but they may be advised to switch back to preventative treatment if they have any episodes of significant bleeding.

Haemophilia A

The preventative treatment for haemophilia A is a drug called *Octocog alfa*.

This is a genetically-engineered version of clotting Factor VIII. Injections every 48 hours are recommended.

Side effects of Octocog alfa are uncommon but can include an itchy skin rash and soreness at the site of the injection.

Haemophilia B

The preventative treatment for haemophilia B is a drug called *Nonacog alfa*.

This is a genetically-engineered version of clotting Factor IX. Injections twice a week are recommended.

Side effects of Nonacog alfa are uncommon, but include headaches, altered taste, nausea and swelling at the injection site.

On-demand treatment

In mild or moderate cases, treatment for haemophilia may only be necessary as an immediate response to bleeding.

Haemophilia A

People with haemophilia A can be treated on-demand with injections of Octocog alfa or a medication called Desmopressin.

Desmopressin is a synthetic hormone which works by stimulating the production of Factor VIII and is usually given by injection. Possible side effects of this medication include headache, stomach pain and nausea.

Haemophilia B

On-demand treatment for haemophilia B usually involves injections of Nonacog alfa.

Living with Haemophilia

It is possible to live with haemophilia and manage the condition in the following ways:

- avoid physical activity that can cause injury and bleeding
- avoid taking blood-thinning medication
- get tested regularly for blood infections
- ask the dentist for advice on how to clean teeth and gums without causing bleeding

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Haemophilia statistics in one year in the UK

Table 1: Number of patients with haemophilia A, registered and treated in one year.

Haemophilia A sufferers	Age range	Severity of haemophilia			
		mild	moderate	severe	total
Total on Register	< 18 years	665	219	826	1 710
	≥ 18 years	1 182	669	3 973	5 824
	Total	1 847	888	4 799	7 534
New Registrations	< 18 years	57	11	58	126
	≥ 18 years	16	4	69	89
	Total	73	15	127	215
Treated in the year	< 18 years	638	173	163	974
	≥ 18 years	1 134	464	701	2 299
	Total	1 772	637	864	3 273

Table 2: New registrations of haemophilia A by age and severity.

Age (years)	Severity of haemophilia			
	mild	moderate	severe	total
0 – 4	52	10	24	86
5 – 9	3	1	13	17
10 – 19	2	0	21	23
20 – 29	13	2	18	33
30 – 39	3	2	11	16
40 – 49	0	0	11	11
50 – 59	0	0	9	9
60 – 69	0	0	8	8
70 – 79	0	0	7	7
80+	0	0	5	5
Total	73	15	127	215

Table 3: Number of units of clotting factor used to treat patients at selected haemophilia centres.

Haemophilia centre	Number of patients treated	Number of units of clotting factor used
Birmingham	39	5 244 750
Bristol	23	4 672 250
Cardiff	10	1 734 750
Edinburgh	11	1 848 000
Glasgow	21	3 720 750
Great Ormond Street Children's Hospital, London	77	19 965 240
Leeds	24	4 905 500
Liverpool	22	2 984 750
Newcastle upon Tyne	16	3 524 500
Oxford	39	8 526 750
Royal London	13	2 234 500
Sheffield	15	2 855 250
Total	310	62 216 990